Efficacy and Safety of Regorafenib in Patients with Characteristics of Good Prognosis in the Treatment of Metastatic Colorectal Cancer: Subgroup Analysis of CORRECT Study

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Eficácia e Segurança de Regorafenibe em Pacientes com Características de Bom Prognóstico no Tratamento do Câncer Colorretal Metastático: Análise de Subgrupo do Estudo CORRECT

Eficacia y Seguridad de Regorafenib en Pacientes con Características de Buen Pronóstico en Tratamiento del Cáncer Colorrectal Metastásico: Análisis de Subgrupo del Estudio CORRECT

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the second most common and when metastatic, it has a five-year survival rate of 14%. Regorafenib is an approved tyrosine kinase inhibitors (TKI) for metastatic colorectal cancer (mCRC) with a proven increase in overall survival (OS). **Objective:** To investigate the efficacy and safety results of regorafenib in patients with mCRC and good prognostic characteristics (GPC). **Method:** Subgroup analysis of the CORRECT study, with participants divided according to GPC, following the criteria: Eastern Cooperative Oncology Group (ECOG) 0, duration of metastatic disease greater than 18 months, up to three metastatic sites and absence of liver metastasis. Efficacy compared with stratified log-rank test and hazard ratios (HR) calculated with the Cox model. **Results:** Of the 760 participants randomized, 292 (34.5%) had GPC; 185 (63.4%) received regorafenib; and 107 (35.6%) received placebo. For the GPC group, the median OS was 10.9 months (95%CI:8.8-12.3) for regorafenib and 7.3 months (95%CI:5.6-9.1) for placebo, with 39% of reduction of the risk of death (HR 0.61; 95% CI:0.43-0.88; p=0.0069). The median progression-free survival (PFS) was 3.5 months (95%CI:3.0-3.9) *versus* 1.8 months (95%CI:1.7-1.8) respectively, with 61% of reduced risk of disease progression or death (HR 0.39; 95%CI:0.30-0.52; p<0.0001). Grade 3 and 4 adverse events were more frequent for regorafenib. After setting baseline for quality of life scores (EQ-5D), these declined less for regorafenib compared to placebo (0.687 versus 0.592) with a significant difference of 0.09. **Conclusion:** GPC patients who received regorafenib improved OS and PFS with less deterioration of quality-of-life compared to placebo.

Key words: protein kinase inhibitors; colorectal neoplasms; neoplasm metastasis; survival analysis.

RESUMO

Introdução: O câncer colorretal (CCR) é o segundo mais incidente e, quando metastático, apresenta taxa de sobrevida de 14% em cinco anos. Regorafenibe é um inibidor de tirosina-quinase (ITQ) aprovado para CCR metastático (CCRm) com aumento comprovado de sobrevida global (SG). **Objetivo:** Explorar resultados de eficácia e segurança de regorafenibe em pacientes com CCRm e características de bom prognóstico (CBP). **Método:** Análise de subgrupo do estudo CORRECT, com participantes divididos de acordo com CBP, seguindo os critérios: *Eastern Cooperative Oncology Group* (ECOG) 0, tempo de doença metastática maior que 18 meses, até três sítios metastáticos e ausência de metástase hepática. Eficácia comparada com teste de log-rank estratificado e *hazad ratios* (HR) calculados com o modelo de Cox. **Resultados:** Dos 760 participantes randomizados, 292 (34,5%) apresentavam CBP; 185 (63,4%) receberam regorafenibe; 107 (35,6%), placebo. Para o grupo CBP, a mediana SG foi 10,9 meses (IC95%:8,8-12,3) para regorafenibe e 7,3 meses (IC95%:5,6-9,1) para placebo, com 39% de redução no risco de morte (HR 0,61; IC95%:0,43-0,88; p=0,0069). A mediana de sobrevida livre de progressão (SLP) foi de 3,5 meses (IC95%:3,0-3,9) *versus* 1,8 mês (IC95%:1,7-1,8) respectivamente, com 61% de redução no risco de progressão da doença ou morte (HR 0,39; IC95%:0,30-0,52; p<0,0001). Os eventos adversos graus 3 e 4 foram mais frequentes para regorafenibe. Após definição de valor basal para escores de qualidade de vida (EQ-5D), estes decaíram menos para regorafenibe comparados com placebo (0,687 *versus* 0,592) com diferença significativa de 0,09. **Conclusão:** Pacientes com CBP que receberam regorafenibe melhoraram SG e SLP com menor deterioração da qualidade de vida comparado com placebo.

Palavras-chave: inibidores de proteínas quinases; neoplasias colorretais; metástase neoplásica; análise de sobrevida.

RESUMEN

Introducción: El cáncer colorrectal (CCR) es el segundo más frecuente y cuando presenta metástasis tiene una supervivencia a los cinco años del 14%. Regorafenib es un inhibidor de la tirosina quinasa (ITQ) aprobado para CCR metastásico (CCRm) con un aumento comprobado en la supervivencia general (SG). **Objetivo:** Explorar los resultados de eficacia y seguridad de regorafenib en pacientes con CCRm y características de buen pronóstico (CBP). **Método:** Análisis de subgrupos del estudio CORRECT, con participantes divididos según CBP, siguiendo los criterios: *Eastern Cooperative Oncology Group* (ECOG) 0, duración de la enfermedad metastásica mayor a 18 meses, hasta tres sitios metastásicos y ausencia de metástasis hepática. Eficacia comparada con la prueba de log-rank estratificada y *hazad ratios* (HR) calculados con el modelo de Cox. **Resultados:** De los 760 participantes aleatorios, 292 (34,5%) tenían CBP; 185 (63,4%) recibieron regorafenib; 107 (35,6%) recibieron placebo. Para el grupo de CBP, la mediana de SG fue de 10,9 meses (IC95%:8,8-12,3) para regorafenib y de 7,3 meses (IC95%:5,6-9,1) para placebo, con una reducción del riesgo de muerte del 39% (HR 0,61; IC95%:0,43-0,88; p=0,0069). La mediana de supervivencia libre de progresión (PFS) fue de 3,5 meses (IC95%:3,0-3,9) frente a 1,8 meses (IC95%:1,7-1,8) respectivamente, con un 61% de riesgo reducido de progresión de la enfermedad o muerte (HR 0,39; IC95%:0,30-0,52; p<0,0001). Los eventos adversos de grado 3 y 4 fueron más frecuentes con regorafenib. Después de establecer la línea de base para las puntuaciones de calidad de vida (EQ-5D), estas disminuyeron menos con regorafenib en comparación con placebo (0,687 frente a 0,592) con una diferencia significativa de 0,09. **Conclusión:** Los pacientes con CBP que recibieron regorafenib mejoraron la SG y la SLP con un menor deterioro en la calidad de vida en comparación con el placebo.

Palabras clave: inhibidores de proteínas quinasas; neoplasias colorrectales; metástasis de la neoplasia; análisis de supervivência.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world accounting for approximately 10% of the total cases. According to GLOBOCAN[1], 1.9 million new cases of cancer were estimated for 2020 worldwide, being considered the second most lethal type of cancer with 935 thousand deaths predicted for the same year[1]. Globally, the epidemiology and burden of CRC vary among the countries. Recently, the incidence and mortality stabilized or declined in middle-to-high Human Development Index (HDI) countries[2]. The drop is usually attributed to early detection and prevention mainly in older adults although this trend masks the rising incidence among young adults[3,4].

Different therapies were developed through the years, improving the survival of these patients. Currently, there are different options of treatment to manage CRC depending on the size of the tumor, location and molecular characteristics, staging, clinical profile of the patient among others. In initial stages, the patients' response to the treatment is high with indication of surgery complemented or not by systemic treatment[5,6]. Patients with localized CRC present 90% 5-year survival. For (mCRC), however, the 5-year survival drops to 14%[7].

Although with early diagnosis, it is estimated that 25% of the patients are diagnosed with metastatic disease and half of the patients with CRC will develop metastases[8]. Further to surgery and radiotherapy, initial treatments are chemotherapy-based (fluoropyrimidine, oxaliplatin and irinotecan, combined or in sequence) and monoclonal antibodies; for refractory disease, regorafenib and TAS-102 are recommended[5].

Regorafenib is an oral multikinase inhibitor that targets tumorigenesis (like KIT, RAF, RET), tumor angiogenesis (VEGFR, TIE2, FGFR and PDGFR) and stromal signaling (PDGFR-ß, FGFR)[9]. Its efficacy and safety to treat mCRC was confirmed in two phase III randomized clinical trials: CONCUR[10] and CORRECT[11]. The study CORRECT[11] showed a significant improvement in global survival (GS) in the regorafenib group than placebo for patients with mCRC treated earlier. This study is registered at ClinicalTrials.gov, numberNCT01103323 and at ClinicalTrialsRegister.eu, number 2009-012787-14.

This study[10] confirmed the efficacy of regorafenib in the Asian population with remarkable improvement of GS. Later, the single arm, open, phase IIIb study CONSIGN[12], with more than 2,700 patients showed that the profile of efficacy and safety was consistent with the data of the CORRECT[11] study.

Despite the confirmed efficacy and safety of regorafenib, the different clinical conditions as the individual characteristics of the disease and of the patient can impact the outcomes from the CRC treatment. Thus, it is important to investigate possible prognostic factors associated with better results in a real-life setting including GS and PFS.

The French study REBECCA[13] on the effectiveness and safety of regorafenib in clinical practice analyzed a cohort of patients with mCRC with baseline characteristics similar to the study CORRECT[11] (population Full Analysis Set-CORRECT (FAS-CORRECT)) whose outcome varied significantly because of specific factors as the Performance Status of the Eastern Cooperative Oncology Group (ECOG-PS), time since diagnosis of the metastatic disease, absence of liver metastasis and number of metastatic sites[13].

These factors were rated to identify the combined defining characteristics of patients with best prognosis and who benefit at the most with regorafenib[13]. Scarce data about its impact on the outcomes of survival and safety are found, even with the current information about the profile of patients with mCRC who most benefit with regorafenib.

The analysis of the subgroup of the study CORRECT[11] aims to evaluate the results of survival and safety of patients with mCRC treated with regorafenib *versus* placebo with characteristics of good prognosis (GP) according to the classification FAS-CORRECT of the population adopted by the study REBECCA[13].

METHOD

Analysis of the subgroup of the study CORRECT, with methodology described by Grothey et al.[11]. The Phase III, double-blind, placebo-controlled randomized study was conducted in 16 countries according to the Declaration of Helsinki based on the International Conference of Harmonization (ICH)[14] and Good Clinical Practices (GCP)[15] and met all local ethical, legal and regulatory demands.

Brazil did not participate but one of the main investigators of the study CORRECT, Prof. Dr. Eric Van Cutsem, is also one of the authors of the analysis of the subgroup and provided the following data[11]: 18 years of age or older patients were eligible after signing the Informed Consent Form, with ECOG-PS of 0 or 1, at least three months of life expectancy and confirmed diagnosis of colorectal adenocarcinoma. They had to have received approved locally standard-therapy and to have disease progression during or within three-months after the last administration of the therapy. Patients who received regorafenib earlier or with unstable medical conditions were excluded.

The patients received best supportive care (BSC), except antineoplastic therapies, randomized in a 2:1 ratio to regorafenib or placebo, 160 mg of regorafenib or placebo once daily for three weeks of each four-week cycle. The therapy was interrupted due to disease progression, toxicity, consent withdrawal, decision of the investigators or death. Patients, investigators and sponsors were blinded, preallocated block design, block size six patients stratified by previous treatment with VEGF-targeting drugs, time from diagnosis of metastatic disease and geographical region.

The patients of the study CORRECT[11] were divided according to the rating criteria from the REBECCA[13] cohort study in a group with GP (score of 0 or 1 and high benefit of GS from regorafenib) and group without GP (score 2 or lower and low benefit with regorafenib). Patients with GP had at least a combination of three of four clinical characteristics: ECOG-PS 0, time from metastatic disease > 18 months, at least three metastatic sites or absence of liver metastasis[13].

The primary outcome was GS, defined as time since randomization up to death by any cause. The secondary outcome included progression-free survival (PFS), defined as time since randomization up to the first clinical or radiologic progression of the disease or death.

RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1[16] was adopted to evaluate the disease progression at each eight weeks for radiologic evaluation or clinical evaluation by the investigator for clinical progression. The safety profile was evaluated as secondary outcome and included the description of adverse events (AE), change of laboratory parameters among others. The grade of AE followed the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[17].

The health-related-quality-of-life (HRQoL) and useful health values were evaluated with the European Organisation for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30)[18], the EuroQol five dimensions (EQ-5D)[19] and the Visual Analogue Scale (VAS)[20]. As a minor difference of the baseline scores of both arms was found, a potential comparison bias, the weighted mean of the initial scores of EQ-5D for regorafenib and placebo arms was calculated and after the result, the value at the end of the treatment was discounted from the mean for each group.

The clinical and demographic characteristics of the patients were analyzed through descriptive statistic with measures of dispersion and central tendencies for continuous variables and percentage for categorical variables. The Kaplan-Meier survival function and the probability of the primary outcome was calculated for each subgroup and the comparisons with the log-rank test. Cox regression model was adopted to calculate the hazard ratio (HR) with confidence interval (CI) of 95%. The level of significance was 5% for two-tailed test, comparisons were made for regorafenib and placebo groups, efficacy analyzes were intention-to-treat based and no imputation occurred for missed evaluations and safety analyzes included all the patients who received at least one dose of the study drug.

RESULTS

Of the 760 patients randomized of the study CORRECT[11] (population intention-to-treat), 292 (34.5%) met the inclusion criteria of GP. Of these, 185 (63.4%) received regorafenib and 107 (35.6%), placebo.

Most of the patients were males with GP (60.5% regorafenib and 63.6% placebo), Whites, (72.4% regorafenib and 72.9% placebo) and mean age of 59.2 (standard deviation [SD] 9.9) for regorafenib and 60.4 years (SD=9.5) for placebo (Table 1).

The majority of the patients presented ECOG score (83.2% in regorafenib and 85.0%, placebo) for clinical characteristics, colon was the primary site of the disease (60% in regorafenib and 65.4%, placebo), with presence of mutation KRAS (55.7% in regorafenib and 58.9%, placebo), in addition to unknown mutation BRAF (88.6% in regorafenib and 86.9%, placebo). The number of metastatic sites was lower than three in more than 90% of the individuals (90.3% in regorafenib and 91.6%, placebo) nearly 50% presented liver metastasis (45.4% in regorafenib and 41.1%, placebo).

Nearly half of the patients received early four or more systemic anticancer therapies (50.3% in regorafenib and 47.7% placebo) and all received bevacizumab.

The sociodemographic characteristics of the group with GP were similar for both groups. The score ECOG 1 for clinical characteristics was found in 65.3% of the patients with regorafenib and 62.8% placebo, in addition to the presence of mutation KRAS (53.1% regorafenib and 63.5% placebo), mutation BRAF unknown and histology of adenocarcinoma in more than 90% of the patients (Table 1).

During follow-up, the number of patients with GP who received at least one subsequent systemic antineoplastic therapy (antineoplastic and immunomodulators agents) was similar in both groups (32.4% regorafenib and 32.7% placebo). But for individuals with GP, 21.9% of the patients in regorafenib received at least one systemic anticancer therapy *versus* 26.4% in placebo (Table 2).

The median GS for patients with GP was 10.9 months (CI95%:8.8-12.3 months) in the arm regorafenib and 7.3 months (CI95%:5.6-9.1 months) in the arm placebo,

showing relative improvement of survival of 3.6 months with reduction of 39% of risk of death (HR 0.61; CI95% 0.43-0.88; *p*=0.0069). The median PFS for regorafenib was 3.5 months (CI95%:3.0-3.9 months) and for placebo was 1.8 months (CI95%:1.7-1.8 months), with reduction of 61% of the risk of disease progression or death (HR 0.39; CI95%:0.30-0.52; *p*<0.0001) when compared to placebo (Figure 1).

Patients with GP in the arm of regorafenib presented reduction of 23% of the risk of death (HR 0.77; CI95%:0.61-0.97; *p*=0.0275) in comparison to placebo, with median GS of 4.8 months (CI95%:4.4-5.6) *versus* 3.8 months in placebo (CI95%:3.4-4.4). In relation to PFS, there was reduction of 45% of the risk of disease progression or death in regorafenib than placebo (HR 0.55; CI95%:0.4-0.67; *p*<0.0001). The median PFS of the

Table 1. Demographic and clinic characteristics of groups with GP and without GP

Characteristics	Patients with GP		Patients without GP	
	Regorafenib (n=185)	Placebo (n=107)	Regorafenib (n=320)	Placebo (n=148)
Age of the patient at randomization (years)				
Mean, SD	59.2 (9.9)	60.4 (9.5)	61.6 (10.2)	59.9 (10.3)
Median (IQR)	59 (52-67)	61 (54-67)	62 (55.0-70.0)	61 (53.0-67.0)
Minimum maximum	34-82	27-85	22-82	25-82
Sex, n (%)				
Male	112 (60.5)	68 (63.6)	199 (62.2)	85 (57.4)
Female	73 (39.5)	39 (36.4)	121 (37.8)	63 (42.6)
Race, n (%)				
White	134 (72.4)	78 (72.9)	258 (80.6)	123 (83.1)
Black	2 (1.1)	4 (3.7)	4 (1.3)	4 (2.7)
Asian	36 (19.5)	19 (17.8)	40 (12.5)	16 (10.8)
Other or unspecified*	13 (7.0)	6 (5.6)	18 (5.6)	5 (3.4)
ECOG. n (%)				
0	154 (83.2)	91 (85.0)	111 (34.7)	55 (37.2)
1	31 (16.8)	16 (15.0)	209 (65.3)	93 (62.8)
Primary site of the disease, n (%)				
Colon	111 (60.0)	70 (65.4)	212 (66.3)	102 (68.9)
Rectum	60 (32.4)	31 (29.0)	91 (28.4)	38 (25.7)
Colorectal	14 (7.6)	6 (5.6)	16 (5.0)	8 (5.4)
Mutation KRAS, n (%)				
No	70 (37.8)	43 (40.2)	135 (42.2)	51 (34.5)
Yes	103 (55.7)	63 (58.9)	170 (53.1)	94 (63.5)
Unknown	12 (6.5)	1 (0.9)	15 (4.7)	3 (2.0)
Mutation BRAF, n (%)				
No	20 (10.8)	13 (12.1)	21 (6.6)	12 (8.1)
Yes	1 (0.5)	1 (0.9)	3 (0.9)	1 (0.7)
Unknown	164 (88.6)	93 (86.9)	296 (92.5)	135 (91.2)
Histology, n (%)				
Adenocarcinoma	182 (98.4)	105 (98.1)	311 (97.2)	140 (94.6)
Adenocarcinoma in situ	0	0	2 (0.6)	3 (2.0)
Adenosquamous carcinoma	0	0	1 (0.3)	1 (0.7)
Carcinoma without other specification	1 (0.5)	1 (0.9)	3 (0.9)	0 (0.0)
Mucinous carcinoma	2 (1.1)	1 (0.9)	3 (0.9)	3 (2.0)
Undifferentiated carcinoma	0	0	0 (0.0)	1 (0.7)

to be continued

Table 1. continuation

Characteristics	Patients with GP		Patients without GP	
	Regorafenib (n=185)	Placebo (n=107)	Regorafenib (n=320)	Placebo (n=148)
Number of previous systemic anticancer therapies (at or after the diagnosis of metastatic disease), n (%)				
1-2	48 (25.9)	21 (19.6)	88 (27.7)	42 (28.3)
3	44 (23.8)	35 (32.7)	80 (25)	37 (25)
≥ 4	93 (50.3)	51 (47.7)	152 (47.3)	69 (46.7)
Anti-VEGF previous treatment, n (%)				
Bevacizumab	185 (100.0)	107 (100.0)	320 (100.0)	148 (100.0)
Patients who discontinued previous treatment due to disease progression, n (%)				
Fluoropyrimidine	80 (43.2)	48 (44.9)	176 (55.0)	87 (58.8)
Bevacizumab	53 (28.6)	35 (32.7)	106 (33.1)	53 (35.8)
Irinotecan	44 (23.8)	33 (30.8)	115 (35.9)	55 (37.2)
Oxaliplatin	46 (24.9)	30 (28.0)	93 (29.1)	47 (31.8)
Panitumumab or cetuximab or both	34 (18.4)	22 (20.6)	65 (20.3)	31 (20.9)
Time since diagnosis of metastases				
Median (months, [IQR])	35.1 (24.9-49.4)	33.6 (24.7-52.6)	26.1 (17.4-40.9)	26.1 (17.3-41.0)
<18 months, n (%)	7 (3.8)	8 (7.5)	84 (26.3)	41 (27.7)
≥18 months, n (%)	178 (96.2)	99 (92.5)	236 (73.8)	107 (72.3)
Number of metastatic sites, n (%)				
<3	167 (90.3)	98 (91.6)	112 (35)	46 (31)
≥3	18 (9.7)	9 (8.4)	208 (65)	102 (69)
Presence of liver metastasis., n (%)				
No	101 (54.6)	63 (58.9)	33 (10.3)	15 (10.1)
Yes	84 (45.4)	44 (41.1)	44 (89.7)	45 (89.9)

Captions: GP = good prognosis; IQR= interquartile range; SD = standard-deviation; ECOG = Eastern Cooperative Oncology Group.
(*) indigenous + native of Alaska + multiple + not informed.

group regorafenib was 1.9 month (CI95%:1.8-1.9 month) *versus* 1.7 month in placebo (CI95%:1.6-1.7 month).

In the group with GP, the arm regorafenib had higher proportion of grade 3 and 4 Treatment Emergent Adverse Events (TEAE), corresponding to 71.7% of all AE; TEAE in the arm placebo occurred in 35.8%. AE grade 5 in both arms had similar proportions (4.9% and 4.7% of all AE reported for regorafenib and placebo, respectively). In addition, 61.4% of AE in the regorafenib group and 7.5% in the placebo group led to dose change. The regorafenib group presented more AE that caused the permanent discontinuation of the drug (9.8% in regorafenib *versus* 0.9% in placebo). The mean time of the treatment with regorafenib was approximately two-fold greater than placebo (median of 4.1 cycles for regorafenib *versus* 2.6 cycles for placebo). The full safety profile is portrayed in Table 3.

Both treatment arms had high proportion of grade 3 and 4 AE for the group without GP (99.4% regorafenib and 98.6%, placebo). For grade 5 AE, regorafenib had lower numbers than placebo (18.4% and 21.8%, respectively). In the regorafenib, 49.7% of the patients had grade 3 or 4 AE and the events requiring dose change were detected in 48.4% of regorafenib *versus* 10.2% placebo. Patients of both groups presented AE which led to the permanent discontinuation of the drug (73% regorafenib and 1.4% placebo).

The initial EORTC QLQ-C30 mean scores for GP were 83.76 (SD=13.16) for patients receiving regorafenib and 85.10 (SD=12.35) for placebo. The mean scores at the end of the treatment were 73.45 (SD=16.72) for regorafenib and 75.30 (SD=16.95) for placebo. The results of EORTC QLQ-C30 are presented in Table 4. For EQ-5D, the initial mean scores were 0.79 (SD=0.21) for regorafenib and 0.82 (SD=0.22) for placebo and at the end, 0.67 (SD=0.29) for regorafenib and 0.64 (SD=0.32) for placebo. The initial scores of VAS of EQ-5D were 70.1 (SD=18.7) for regorafenib and 69.8 (SD=18.3) for placebo and at the end, 60.4 (SD=20.5) and 59.4 (SD=21.9), respectively.

Table 2. Subsequent systemic anticancer therapy of patients with GP and without GP

Characteristics	Patients with GP		Patients without GP	
	Regorafenib (n=185)	Placebo (n=107)	Regorafenib (n=320)	Placebo (n=148)
Number of individuals (%) with one medication at least, n (%)	60 (32.4)	36 (33.6)	71 (22.2)	40 (27.0)
Antineoplastic and immunomodulators agents, n (%)	60 (32.4)	35 (32.7)	70 (21.9)	39 (26.4)
Anthracyclines and related substances	2 (1.1)	0	0	0
Antimetabolites	4 (2.2)	0	1 (0.3)	0
Antineoplastic agents	8 (4.3)	4 (3.7)	3 (0.9)	3 (2.0)
Combinations of antineoplastic agents	0	2 (1.9)	0	2 (1.4)
Folic acid and analogues/derivates	13 (7.0)	11 (10.3)	18 (5.6)	12 (8.1)
Monoclonal antibodies	21 (11.4)	11 (10.3)	18 (5.6)	11 (7.4)
Nitrogen mustard analogues	2 (1.1)	0	1 (0.3)	0
Other alkylating agents	1 (0.5)	0	2 (0.6)	1 (0.7)
Other antineoplastic agents	9 (4.9)	8 (7.5)	6 (1.9)	10 (6.8)
Other cytotoxic antibiotics	19 (10.3)	11 (10.3)	19 (5.9)	18 (12.2)
Other vegetal alkaloids and natural products	0	1 (0.9)	0	0
Platinum compounds	13 (7.0)	8 (7.5)	22 (6.9)	6 (4.1)
Pyrimidine analogues	42 (22.7)	23 (21.5)	52 (16.3)	29 (19.6)
Inhibitors of kinase protein	0	0	3 (0.9)	0
Dermatologic	0	1 (0.9)	0	0
Musculoskeletal system	0	1 (0.9)	0	1 (0.3)
Experimental drugs	1 (0.5%)	0	1 (0.3%)	0
Not classified	0	1 (0.9)	0	1 (0.7)

Captions: GP = good prognosis.

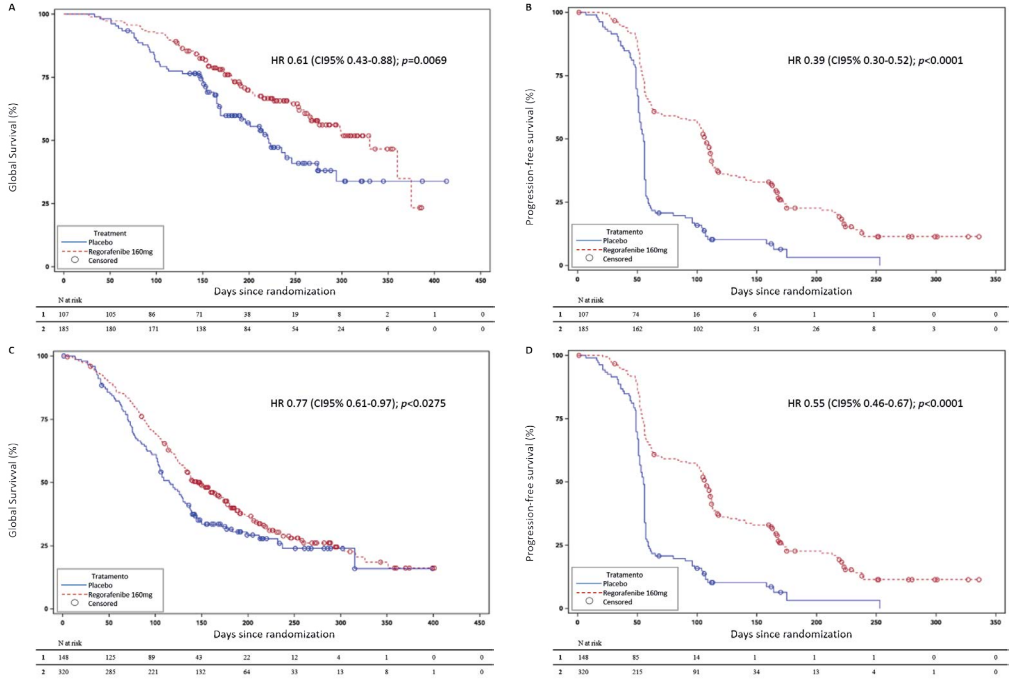

Figure 1. Analyzes of GS and PFS Kaplan-Meier of patients of the subgroups. (A) GS and (B) PFS of patients with GP treated with regorafenib or placebo; (C) GS e (D)

Captions: HR = hazard ratio; CI = confidence interval.
Note: Log-rank test estimated *p* values.

When a slight difference among the initial values for both arms was detected, the weighted mean of the EQ-5D was calculated. After the definition of the common initial value for each group, the result at the end of the treatment was discounted from the initial value for placebo and regorafenib: -0.110 (SD=0.260) and -0.205 (SD 0.292), respectively. The final scores at the end of the treatment of 0.687 for regorafenib and 0.592 for placebo were calculated and a lower decline of the quality-of-life for regorafenib was made evident. The difference of 0.095 between regorafenib and placebo for patients with GP is clinically significant, above the minimally important

Table 3. Treatment Emergent Adverse Events which occurred in ≥5% of both GP groups since the beginning of the treatment until 30 days after its end (safety population)

	Patients with GP					
	Regorafenib (n=184)			Placebo (n=106)		
Adverse Event	**Any Grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**
Any adverse event, n (%)	**184 (100)**	**114 (62)**	**18 (9.8)**	**100 (94.3)**	**33 (31.1)**	**5 (4.7)**
Fatigue	76 (41.3)	15 (8.2)	0	32 (30.2)	5 (4.7)	0
Asthenia	47 (25.5)	6 (3.3)	0	17 (16)	2 (1.9)	0
Skin rash of mouth-foot	99 (53.8)	37 (20.1)	0	6 (5.7)	0	0
Diarrhea	89 (48.4)	20 (10.9)	0	19 (17.9)	2 (1.9)	0
Anorexia	77 (41.8)	3 (1.6)	0	22 (20.8)	4 (3.8)	0
Voice changes	69 (37.5)	0	0	9 (8.5)	0	0
Hypertension	69 (37.5)	17 (9.2)	0	12 (11.3)	2 (1.9)	0
Mucosa inflammation	25 (13.6)	2 (1.1)	0	2 (1.9)	0	0
Oral mucositis	41 (22.3)	5 (2.7)	0	2 (1.9)	0	0
Rash or desquamation	60 (32.6)	13 (7.1)	0	4 (3.8)	1 (0.9)	0
Nausea	49 (26.6)	0	0	19 (17.9)	2 (1.9)	0
Weight loss	57 (31)	20 (10.9)	1 (0.5)	9 (8.5)	0	0
Fever	59 (32.1)	5 (2.7)	0	13 (12.3)	0	0
Dry skin	17 (9.2)	0	0	6 (5.7)	0	0
Alopecia	18 (9.8)	0	0	2 (1.9)	0	0
Taste change	18 (9.8)	0	0	2 (1.9)	0	0
Vomit	28 (15.2)	2 (1.1)	0	13 (12.3)	0	0
Sensory neuropathy	11 (6.0)	1 (0.5)	0	3 (2.8)	0	0
Nasal bleeding	14 (7.6)	0	0	1 (0.9)	0	0
Dyspnea	24 (13)	2 (1.1)	1 (0.5)	14 (13.2)	5 (4.7)	0
Cough	23 (12.5)	2 (1.1)	0	13 (12.3)	0	0
Back pain	26 (14.1)	1 (0.5)	0	10 (9.4)	0	0
Muscle pain	10 (5.4)	2 (1.1)	1 (0.5)	2 (1.9)	0	0
Headache	27 (14.7)	1 (0.5)	0	5 (4.7)	0	0
Pain, abdomen	33 (17.9)	1 (0.5)	0	18 (17.0)	1 (0.9)	0
Constipation	38 (20.7)	0	0	14 (13.2)	0	0
Thrombocytopenia	12 (6.5)	3 (1.6)	2 (1.1)	1 (0.9)	0	0
Hyperbilirubinemia	11 (6.0)	3 (1.6)	0	0	0	0
Increased ALT	11 (6.0)	3 (1.6)	1 (0.5)	4 (3.8)	0	0
Increased AST	12 (6.5)	5 (2.7)	4 (2.2)	5 (4.7)	2 (1.9)	0
Increased Lipase	14 (7.6)	8 (4.3)	2 (1.1)	0	0	0
Proteinuria	16 (8.7)	4 (2.2)	0	1 (0.9)	0	0
Anemia	21 (11.4)	10 (5.4)	0	4 (3.8)	1 (0.9)	0

to be continued

Table 3. continuation

	Patients without GP					
	Regorafenib (n=316)			Placebo (n=147)		
Adverse Event	Any Grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event, n (%)	**287 (90.8)**	**149 (47.2)**	**8 (2.5)**	**96 (65.3)**	**19 (12.9)**	**3 (2)**
Fatigue	83 (26.3)	15 (4.7)	2 (0.6)	27 (18.4)	4 (2.7)	1 (0.7)
Asthenia	60 (19)	16 (5.1)	0	15 (10.2)	5 (3.4)	0
Skin rash of mouth-foot	124 (39.2)	46 (14.6)	0	12 (8.2)	0	0
Diarrhea	99 (31.3)	18 (5.7)	1 (0.3)	12 (8.2)	1 (0.7)	0
Anorexia	96 (30.4)	14 (4.4)	0	26 (17.7)	5 (3.4)	0
Voice changes	76 (24.1)	0	0	6 (4.1)	0	0
Hypertension	77 (24.4)	19 (6)	0	6 (4.1)	0	0
Mucosa inflammation	51 (16.1)	9 (2.8)	0	1 (0.7)	0	0
Oral mucositis	41 (13)	7 (2.2)	0	4 (2.7)	0	0
Rash or desquamation	44 (13.9)	11 (3.5)	0	4 (2.7)	0	0
Nausea	40 (12.7)	2 (0.6)	0	17 (11.6)	0	0
Weight loss	40 (12.7)	0	0	4 (2.7)	0	0
Fever	23 (7.3)	1 (0.3)	0	5 (3.4)	0	0
Dry skin	19 (6)	0	0	1 (0.7)	0	0
Alopecia	19 (6)	0	0	0	0	0
Taste change	20 (6.3)	0	0	4 (2.7)	0	0
Vomit	22 (7)	2 (0.6)	0	8 (5.4)	0	0
Sensory neuropathy	4 (1.3)	0	0	0	0	0
Nasal bleeding	26 (8.2)	0	0	5 (3.4)	0	0
Dyspnea	18 (5.7)	0	0	2 (1.4)	0	0
Cough	7 (2.2)	0	0	2 (1.4)	0	0
Back pain	37 (11.7)	4 (1.3)	0	15 (10.2)	3 (2)	1 (0.7)
Muscle pain	7 (2.2)	1 (0.3)	0	4 (2.7)	1 (0.7)	0
Headache	11 (3.5)	2 (0.6)	0	6 (4.1)	0	0
Pain, abdomen	0	0	0	0	0	0
Constipation	27 (8.5)	0	0	9 (6.1)	0	0
Thrombocytopenia	19 (6)	4 (1.3)	0	3 (2)	1 (0.7)	0
Hyperbilirubinemia	16 (5.1)	4 (1.3)	0	1 (0.7)	1 (0.7)	0
Increased ALT	5 (1.6)	3 (0.9)	0	0	0	0
Increased AST	12 (3.8)	4 (1.3)	0	1 (0.7)	0	0
Increased Lipase	14 (4.4)	5 (1.6)	4 (1.3)	3 (2.0)	1 (0.7)	1 (0.7)
Proteinuria	18 (5.7)	4 (1.3)	0	4 (2.7)	1 (0.7)	0
Anemia	9 (2.8)	4 (1.3)	1 (0.3)	5 (3.4)	1 (0.7)	0

Captions: GP = good prognosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

difference of 0.07[21]. Additionally, the pre-progression score was calculated through the weighted mean of all the cycles before the final cycle of treatment, reaching 0.745 for regorafenib and 0.757 for placebo.

The mean scores of EORTC QLQ-C30 for the group without GP initially were 76.52 (SD=16.25) for regorafenib and 77.34 (SD=16.25) for placebo and at the end of the treatment, 64.60 (SD=18.97) and 69.92 (SD=18.72), respectively. The results of the global health status and the scores of physical functioning according to EORTC QLQ-C30 are presented in Table 4. The initial mean scores of EQ-5D for the group without GP were 0.69 (SD=0.27) for regorafenib and 0.68 (SD=0.29) for placebo and at the end, 0.54 (SD=0.32) and 0.54 (SD=0.36), respectively. The mean initial scores of VAS of EQ-5D were 62.6 (SD=19.5) for regorafenib and 63.0 (SD=21.5) for placebo and at end, 52.4 (SD=19.8) and 55.4 (SD=21.3), respectively (Table 4).

DISCUSSION

The patients with GP who received regorafenib were evaluated with placebo to find if better results would be reached at the end of the treatment[11] in the analysis of the subgroup of the study CORRECT. As the study REBECCA[13] pointed out, individuals with lower ECOG-PS scores, more time since diagnosis of metastasis, less than three metastatic sites and absence of liver metastasis had better survival after the treatment with regorafenib and according to the present conclusions[13], these characteristics have positively impacted the outcome of efficacy and were utilized in the present analysis of subgroup for patients with and without GP[13]. The medians of GS and PFS improved for patients with GP than without GP as aforementioned[13]. In addition, patients treated with regorafenib had better efficacy for both groups with and without GP than placebo as reported by the studies CONCUR[10] and CORRECT[11].

In addition to REBECCA[13], other real-life studies produced evidences to support the selection of the population treated with regorafenib who improved GS. The studies of Aljubran et al.[22], Novakova-Jiresova et al.[23] and Yamaguchi et al.[24] have also demonstrated that low ECOG-OS scores and time of diagnosis ≥18 months of metastatic disease are variables which have positively influenced GS and PFS with regorafenib.

The high proportion of AE in regorafenib patients as found in this analysis may have been impacted by

Table 4. Patients' quality-of-life

Questionnaire of quality-of-life	Regorafenib with GP		Placebo with GP	
	First cycle	End of the treatment	First cycle	End of the treatment
EQ-5D (mean±SD)	0.79 ± 0.21	0.67±0.29	0.82 ± 0.22	0.65 ± 0.32
EQ-EVA (mean±SD)	70.13 ± 18.72	60.43 ± 20.50	69.80 ± 18.34	59.39 ± 21.86
EORTC Summary Score QLQ-C30 (mean±SD)	83.76 ± 13.16	73.45 ± 16.72	85.10 ± 12.35	75.30 ± 16.95
EORTC QLQ-C30 – Global health status (mean±SD)	69.67 ± 19.27	52.36 ± 21.91	69.55 ± 20.90	55.36 ± 24.12
EORTC QLQ-C30 – Physical functioning (mean±SD)	82.77 ± 16.55	73.33 ± 23.60	85 ± 16.4	74.52 ± 24.21
Questionnaire of quality-of-life	**Regorafenib without GP**		**Placebo without GP**	
	First cycle	**End of the treatment**	**First cycle**	**End of the treatment**
EQ-5D (mean±SD)	0.69 ± 0.27	0.54 ± 0.32	0.68 ± 0.29	0.54 ± 0.36
EQ-EVA (mean±SD)	62.55 ± 19.51	52.37 ± 19.82	62.96 ± 21.48	55.39 ± 21.32
EORTC QLQ-C30 Summary Score (mean±SD)	76.52 ± 16.25	64.60 ± 18.97	77.34 ± 16.25	69.62 ± 18.72
EORTC QLQ-C30 – Global health status (mean±SD)	58.55 ± 21.93	46.78 ± 21.21	61.09 ± 22.86	48.54 ± 23.42
EORTC QLQ-C30 – Physical functioning (mean±SD)	75.28 ± 20.79	60.41 ± 26.56	75.95 ± 20.90	63.86 ± 29.46

Captions: GP = good prognosis; SD = standard deviation; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality-of-Life Questionnaire; EQ-5D = European Quality of Life Five Dimension; VAS = visual analogue scale.

the longer duration of the treatment than placebo, not forgetting that the CORRECT[11] study was conducted in 2011 and later, strategies to improve the safety and quality-of-life profile with regorafenib were implemented with reduced dose at the beginning of the treatment or discontinuation of the treatment after grade 3 AE and initial dose scheduling in the first cycle of treatment[10-13,25].

The study ReDOS[25] with dose scheduling found lower incidence of high-grade AE during cycle 1 and improvement of the scores of quality-of-life with means significantly better in week 2 in the group of dose scheduling than standard-dose for fatigue, interference in general activities, mood, walk and regular labor activities, suggesting that the strategy of dose scheduling benefits the patient's quality-of-life[25]. The data of the current analysis corroborate the existence of lower decline of the quality-of-life for patients with GP who utilized regorafenib than placebo.

Similar percentages of patients able to receive at least one subsequent antineoplastic treatment (32.7% for placebo and 32.4% for regorafenib) were found in the GP group and higher percentage of GP patients in regorafenib received subsequent systemic antineoplastic treatment than without GP in regorafenib (32.4% *versus* 21.9% respectively), which reinforces the importance of the treatment with regorafenib for GP patients to favor better improvement of GS and possibility of continuing the treatment.

At last, mCRC is a condition with 5-year estimate survival in 14% of the cases and few available alternatives exist to treat refractory patients[26]. Thus, regorafenib is listed as an option of treatment in international and national guidelines based in pivotal studies, including alternative approaches of initial dose with survival comparable and low incidence of AE[5,6,25]. Regorafenib is approved since 2012 worldwide[27].

It was possible to notice from the present analysis that certain clinical characteristics positively impact the GS and PFS of patients to be treated with regorafenib, corroborating the existing literature. These findings can impact clinical practice, offering better understanding of which patients can best benefit with regorafenib, supporting evidence-based public policies.

Although better results have been found for individuals with GP, regorafenib continues as an effective option for patients who did not present these specific clinical characteristics, mainly when refractory to early standard-therapies. To address safety issues, the strategy of dose scheduling together with preventive and proactive measures improves the frequency of AE and the quality-of-life that encourages the patient to adhere to the treatment[28].

CONCLUSION

Patients with mCRC and GP with at least three of the four clinical characteristics (ECOG-PS score 0, up to three tumor sites, ≥18 months since the diagnosis of the metastatic disease and without liver metastasis) in the current analysis of the subgroup of the study CORRECT, had better SG and PFS and low decline of the quality-of-life with regorafenib than placebo.

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CONTRIBUTIONS

Rodrigo Palhares, Glauco Britto, Yun Su, Marie-Aude Le Berre, Ricardo Saad, Fabricio Navachi, Daniela Foli, Helene Ostojic and Graziella Azevedo contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. Eric Van Cutsem contributed substantially to the study design, acquisition, analysis and interpretation of the data. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

The authors Rodrigo Resende Palhares, Glauco do Canto Britto, Yun Su, Marie-Aude Le Berre, Ricardo Saad Henriques, Fabricio Volpato Navachi, Daniela Cristina Foli Pereira, Helene Ostojic and Graziella Agostini Azevedo have competing interests as Bayer collaborators. Eric Van Cutsem has competing interests as a consultant/advisor of Array BioPharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, halozima, Lilly, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche and SERVIER.

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